PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/70

A1

(11) International Publication Number: **WO 98/17280**

(43) International Publication Date: 30 April 1998 (30.04.98)

(21) International Application Number: PCT/GB97/02862

(22) International Filing Date: 17 October 1997 (17.10.97)

(30) Priority Data:

9621771.6	18 October 1996 (18.10.96)	GB
028,693	18 October 1996 (18.10.96)	US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD OF TREATMENT OF HEART DISEASE CAUSED BY CHLAMYDIA PNEUMONIAE

(57) Abstract

A method of combatting atherosclerosis, said method comprising administering an effective amount of a macrolide antibiotic, for example an azalide such as azithromycin, optionally together with one or more pharmaceutically acceptable carriers or excipients, to a subject.

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METHOD OF TREATMENT OF HEART DISEASE CAUSED BY CHLAMYDIA PNEUMONIAE

FIELD OF THE INVENTION

This invention relates to the treatment of heart disease, more particularly to the use of certain antibiotics in combatting atheroscelorsis.

DESCRIPTION OF THE PRIOR ART

Coronary heart disease is the largest single cause of premature death in the western world, and in the UK alone is responsible for about 160,000 deaths annually. The traditional view held by a significant proportion of the medical profession is that age and social and economic factors are the predominant causes of heart disease. In recent years, however, there has been a significant number of reports implicating certain bacteria in coronary heart disease, although these have met with considerable scepticism in some quarters.

Bacteria referred to in such reports include *Helicobacter pylori* and *Chlamydia pneumoniae*. Thus, for example, Finnish researchers in the late 1980s reported that coronary heart disease sufferers were more likely to have high levels of antibodies to the *Chlamydia pneumoniae* bacterium than healthy people (The Lancet, 1988: 983-986). More recently, the organism itself has been found in atherosclerotic arteries of patients undergoing abdominal aortic aneurysm repair (J. Clin. Pathol., 1996, 49(2): 102-106). In the Journal of the American College of Cardiology, June 1996, 27(7): 1555-61, it was reported that 79% of patients undergoing surgery to excise atherosclerotic plaques showed an antibody to *Chlamydia pneumoniae* active in the lesions, but that only 4% of non-atherosclerotic pathology specimens showed the same antibody. It was alleged on this basis that the bacterium may be specifically linked with atheroma and not with other causes of arterial

damage.

Other workers have reported similar findings, and it has been suggested that inflammation associated with persistent bacterial infection of arterial walls could trigger an immune reaction which raises fibrinogen and tissue factor levels in the blood and increases the potential for atherothrombosis.

However, there is still considerable scepticism about this theory within the medical profession, particularly amongst cardiologists, and many workers doubt whether *Chlamydia pneumoniae* is present in the diseased heart at all or, if it is, it is merely there as an innocent bystander. Thus, in the Journal of Infectious Diseases, 1996, 173(4): 957-62 it was reported that a research team had failed to culture *Chlamydia pneumoniae* from 58 samples of atheroma. Opinions are therefore firmly divided on the role, if any, of *Chlamydia pneumoniae* in heart disease.

The present invention is based on the unexpected finding that administration of certain antibiotics, more specifically macrolide antibiotics such as azithromycin, may lead to a reduction in markers of blood clotting and inflammation in the blood of post-myocardial infarction patients, possibly through eradication of underlying *Chlamydia pneumoniae* infection. Such administration of macrolide antibiotics may therefore be beneficial not only to cardiac patients, for example by reducing inflammation of heart tissue, blood clotting, susceptibility to angina, the likelihood of re-admissions and/or need for bypass or other surgery, but also prophylatically to patients in general.

SUMMARY OF THE INVENTION

Thus viewed from one aspect the present invention provides a method of combatting atherosclerosis, said method comprising administering an effective amount of a macrolide antibiotic, for example an azalide, optionally together with one or more pharmaceutically acceptable

carriers or excipients, to a subject.

In the method according to the invention, the macrolide antibiotic may if desired be administered with other useful agents such as platelet aggregation inhibitors, blood thinning agents, and/or lipid lowering agents. Thus in a further aspect, the present invention provides a composition for combatting atherosclerosis, the composition comprising a macrolide antibiotic or a derivative thereof, e.g. azithromycin together with one or more of the agents selected from the group consisting of platelet aggregation inhibitors, blood thinners, and/or lipid-lowering agents etc, optionally together with one or more carriers or excipients.

Viewed from a further aspect the present invention provides the use of a macrolide antibiotic e.g. azithromycin or a derivative thereof for the preparation of a composition for use in combatting atherosclerosis.

As is well known, macrolide antibiotics are characterised by the presence of a macrocyclic lactone ring to which one or more sugar molecules are attached. Representative examples of such antibiotics include erythromycin, spiramycin, oleandomycin, clarithromycin, dirithromycin, roxithromycin, josamycin, kitasamycin, midecamycin, miocamycin, rokitamycin, rosaramicin, azithromycin and derivatives thereof, e.g. salts such as phosphates and esters such as acetates.

Azithromycin [(2R, 3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R)-13-(2,6-Dideoxy-3-C-3-O-dimethyl-α-L-ribohexopyranosyloxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-(3,4,6-trideoxy-3-dimethylamino-β-D-xylohexopyranosyloxy)-1-oxa-6-azacyclopentadecan-15-one], available commercially in the dihydrate form as Zithromycin®, is a preferred macrolide or azalide antibiotic for use in accordance with the invention, having proved effective using single daily dosages over periods as short as three days. It will be appreciated that such simple dosage regimens are highly advantageous in securing patient compliance.

periods as short as three days. It will be appreciated that such simple dosage regimens are highly advantageous in securing patient compliance.

A typical daily dose of a macrolide antibiotic such as azithromycin will be 500 mg given orally, for example for up to 3 days, although other dosages and methods of administration may if desired by employed. It may be advantageous to administer a second course of the antibiotics some time, e.g. one, two or three months, after the first course in order to maximise the effect of the treatment. It may be even more advantageous to administer further courses of the antibiotic at intervals of one, two or three months after the second course in order to sustain the benefit. Typically this may be carried out for up to a year after the initial course has been administered.

The invention will now be described in a non-limiting manner by way of example:

Example 1

A randomised double-blind study was conducted in which 60 male post-myocardial infarction patients were treated with azithromycin (500 mg per day, given orally for 3 days) or placebo. A further blinded course of azithromycin or placebo was given to 45 of the patients after a further 3 months. The results showed that azithromycin, particularly after double therapy, led to significant reduction in *Chlamydia pneumoniae* antibody titres (IgG) and to reduced levels of monocyte tissue factor, CD11b expression and serum markers of hypercoagulation and inflammation such as total leucocyte count and serum neopterin.

Example 2

The relationship between antibodies against *anti-Chlamydia pneumoniae* (Cp) and future cardiovascular events in male survivors of myocardial infarction (MI)

was explored. The effect of azithromycin antibiotic therapy was assessed in a subgroup of post-MI patients.

Between February 1995 and September 1995, 220 consecutive male patients attending a post-MI outpatient clinic at St George's Hospital, London were enrolled. Patients were screened for serum IgG antibodies against Cp by a microimmunofluorescence assay with elementary bodies of Cp strain IOL-207 as test antigen. Patients with chronic bronchitis, those currently taking macrolide antibiotics, and those with MI within the preceding 6 months (to ensure resolution of immune responses caused by infarction) were excluded. Also excluded were any subjects with serum that cross-reacted with *Chlamydia trachomatis* or *Chalmydia psitticai* antigens. Patients were stratified into one of three anti-Cp antibody titre groups: group Cp-ve (n=59), no detectable anti-Cp antibodies (seronegative); group Cp-I (n=74), seropositive at a serum dilution of between 1/8 and 1/32; and group Cp+ve (n=80), seropositive at a serum dilution of ≥1/64. Anti-Cp antibody titres were remeasured after 3 months in the latter group. Patients with Cp titre (≥1 in 64) on both occasions were entered in a double-blind placebo-controlled study of the effects of azithromycin therapy (either 500 mg/d for 3 days or two such courses 3 months apart) on anti-Cp titre and hemostatic and inflammatory markers in post-MI patients. These patients had their anti-Cp titre and other markers tested at 3 and at 6 months.

Adverse cardiovascular events (defined as the first admission to hospital with nonfatal MI; unstable angina requiring either intravenous anti-anginal therapy, coronary angioplasty, or urgent coronary artery bypass surgery; or cardiovascular death) were monitored for 18 months from the original Cp titre determination. The information was obtained from patients' clinic visits, telephone enquiries, case notes, and hospital computerised records.

Statistical Analysis

The frequency of adverse events was assessed in groups Cp-ve, Cp-I and Cp+ve. Additionally, Cp+ve patients were further divided into three subgroups: Cp+ve-NR, patients who did not enter the antibiotic study; Cp+ve-P, patients who were randomized to receive placebo medication; and Cp+ve-A, patients who were given either a single or double course of azithromycin.

The proportion of patients experiencing an adverse event was compared between group Cp-ve and all other groups by use of the χ^2 test. The ORs for adverse cardiovascular events in each Cp+ve group relative to group Cp-ve were calculated by use of a multiple logistic regression model before and after adjustment for age, diabetes mellitus, hypertension, hyperlipidemia, smoking status (current, ever, or never) and previous coronary artery bypass surgery or percutaneous transluminal coronary angioplasty (STATA analysis). A value of $P<.05$ was considered significant.

Results

Seven patients were excluded because their sera cross-reacted with other chlamydial species; analysis is hence based on the remaining 213 patients. Table 1 shows the baseline clinical characteristics. Patients with persisting seropositivity of ≥1/64 were randomized to either oral azithromycin (Cp+ve-A, 500 mg/d for 3 days [n=28] or 500 mg/d for 6 days [n=12]) or placebo (Cp+ve-P, n=20). Of the remaining 12 patients, 7 were unwilling to enter the trial, and 5 had other serious medical conditions that prevented their inclusion.

Table 1 - Patient Characteristics and Incidence of Cardiovascular Events at a Mean of 18±4 Months of Follow-up

Group	Cp-ve (n=59)	Cp-I (n=74)	Cp+ve-NR (n=20)	Cp+ve-P (n=20)	Cp+ve-A (n=40)
Age, y(mean±SD)	63±8	61±9	63±9	60±9	58±7
Diabetes mellitus, n(%)	6(10)	9(12)	6(30)	8(40)	12(30)
Hypertension, n(%)	15(25)	9(12)	3(15)	4(20)	7(18)
Previous PTCA or CABG, n(%)	12(20)	20(27)	8(40)	6(30)	12(30)
Hyperlipidemia, n(%)	23(39)	31(42)	10(50)	7(35)	18(45)
Smoking (past), n(%)	39(66)	40(54)	14(70)	10(50)	21(53)
Smoking (current), n(%)	7(12)	16(22)	3(15)	5(25)	14(35)
Months since MI, mean±SD	44±14	44±27	46±32	39±24	47±32
Anterior MI, %	53	53	50	58	53
Ejection fraction, %	41±14	45±13	41±19	47±14	48±14
Adverse cardiovascular events, n					
Death	0	0	1	1	1
Unstable angina/MI	0	7	4	4	2
PTCA/CABG	4	4	1	0	0
Total (%)	4(7)	11(15)	6(30)	5(25)	3(8)
χ^2 vs Cp-ve		2.1	7.3	4.9	0.9
p		.1	.007	.03	NS

Cp-ve indicates seronegative group of patients; Cp-I, group with intermediate antibody titres; Cp+ve-NR/P, group with elevated antibody titres either randomized to placebo or not randomized; Cp+ve-A, group with elevated antibody titres randomized to azithromycin; PTCA, percutaneous transluminal coronary angioplasty; and CABG, coronary artery bypass surgery.

At 6 months, in the patients participating in the antibiotic trial, anti-Cp titre fell to ≤1/16 in 43% of patients (17 of 40) receiving azithromycin compared with only 10% patients (2 of 20) taking placebo (P=.02). The ORs for adverse cardiovascular events are shown for all groups in Table 2. The frequency of adverse events increased with rising anti-Cp titre, which persisted after correction for confounding variables. Because there were no significant differences in cardiovascular risk factors or events between the Cp+ve-NR and Cp+ve-P groups, results of the two groups were combined in the calculation of the ORs. The rate of further cardiovascular events in the Cp+ve-A group was similar to that in the Cp-ve group (8% versus 7%; OR, 0.9; P=NS). Compared with patients in the combined placebo/ nonrandomized group, the azithromycin-treated group had a fivefold reduction in cardiovascular events, with an OR of 0.2 (95% confidence interval, 0.05 to 0.8; P=.03). There was no difference between the patients receiving either single or double azithromycin course in the proportion having a decrease in anti-Cp titre or the cardiovascular event rate.

Table 2 - ORs for CV Events in Seronegative and Seropositive Patient Groups

Group	Total CV Events, n(%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Cp-ve(n=59)	4(7)		
Cp-I(n=74)	11(15)	2.4(0.7-8.0)	2.0(0.6-6.8)
Cp+VE-NR/P(n=40)	11(28)	5.2(1.5-17.8)*	4.2(1.2-15.5)†
Cp+ve-A(n=40)	3(8)	1.1(0.2-5.3)	0.9(0.2-4.6)

See Table 1 for explanation of group designations

Comparisons of cardiovascular (CV) events are for all groups relative to group Cp-ve (expressed as OR (95% confidence interval [CI]). Adjusted OR calculated after controlling for the following variables: age, diabetes mellitus, smoking status, hypertension, hyperlipidemia and previous coronary revascularization.

*P=.008,

+.03 vs group Cp-ve.

CLAIMS

1. A method of combatting atherosclerosis, said method comprising administering an effective amount of azithromycin or a derivative thereof, optionally together with one or more pharmaceutically acceptable carriers or excipients, to a subject.

2. A method as claimed in claim 1 wherein a second effective amount of azithromycin is administered about one month after administration of a first effective amount of azithromycin.

3. A method as claimed in claim 2 wherein one or more further effective amounts of azithromycin are added at intervals of one month or more.

4. Use of azithromycin or a derivative thereof for the prepartion of a medicament for use in combatting atherosclerosis.

INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/GB 97/02862

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 22819 A (BOARD OF REGENTS OF THE UNIVERSITY OF WASHINGTON) 23 December 1992 see page 3, line 31 - line 35 see page 9, line 9 - line 34 see page 16, line 23 - line 28 see page 22 see page 25 lines 33-34,37-39 ---	1-4
X	MARRIE: "Chlamydia pneumoniae" THORAX, vol. 48, no. 1, 1993, see page 2, right-hand column see page 3 ---	1,4
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 1998	11.03.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COOK : "Chlamydia pneumoniae" J. ANTIMICROB. CHEMOTHER., vol. 34, no. 6, December 1994, pages 859-73, XP002056252 see page 865	1,4

X	COOK: "Clinical aspects of Chlamydia pneumoniae infection" PRESSE MED. (FR.), vol. 24, no. 5, 4 February 1995, pages 278-282, XP002056253 see page 280, right-hand column see page 281	1,4

X	VALTONEN: "Symposium graft infection sponsored by the Sanofi-Chinoin Co: the causative role of Chlamydia pneumoniae and other bacteria in the development of coronary heart disease" INT. ANGIOLOGY, vol. 15, no. 2sup1, May 1996, page 61 XP002056254 abstract nr 034	1,4

X	BLANCHARD: "Chlamydia infections" BR. J. CLIN. PRACT., vol. 48, no. 4, 1994, pages 201-205, XP002056255 see page 202; table 1 see page 203, left-hand column see page 204, left-hand column	1,4

X	GAYDOS: "Chlamydia pneumoniae: a review and evidence for a role in coronary artery disease" CLIN. MICROBIOL. NEWSLETTER, vol. 17, no. 7, 1995, pages 49-54, XP002056256 see page 51	1,4

P,X	STILLE: "Argumente für eine Antibiotika-Therapie der Atherosklerose" CHEMOTHER. J., vol. 6, no. 1, 21 April 1997, pages 1-5, XP002056257 see the whole document	1,4

1

INTERNATIONAL SEARCH REPORT

Inte. .ional application No.
PCT/GB 97/02862

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-3
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-3 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9222819 A	23-12-92	AU 2249892 A	12-01-93
		US 5424187 A	13-06-95
		ZA 9206713 A	09-03-93

(19)日本国特許庁（ＪＰ）　(12) 公表特許公報（Ａ）　(11)特許出願公表番号
特表2002－508738
（P2002－508738A）
(43)公表日　平成14年３月19日(2002.3.19)

(51)Int.Cl.'	識別記号	ＦＩ	ﾃｰﾏｺｰﾄﾞ(参考)
Ａ６１Ｋ　31/7048		Ａ６１Ｋ　31/7048	
Ａ６１Ｐ　9/00		Ａ６１Ｐ　9/00	
9/10		9/10	

審査請求　有　　予備審査請求　有　（全 15 頁）

(21)出願番号　特願平10－519090
(86)（22)出願日　平成９年10月17日(1997.10.17)
(85)翻訳文提出日　平成11年４月19日(1999.4.19)
(86)国際出願番号　ＰＣＴ／ＧＢ９７／０２８６２
(87)国際公開番号　ＷＯ９８／１７２８０
(87)国際公開日　平成10年４月30日(1998.4.30)
(31)優先権主張番号　９６２１７７１．６
(32)優先日　平成８年10月18日(1996.10.18)
(33)優先権主張国　イギリス（ＧＢ）
(31)優先権主張番号　６０／０２８，６９３
(32)優先日　平成８年10月18日(1996.10.18)
(33)優先権主張国　米国（ＵＳ）

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最終頁に続く

(54)【発明の名称】　クラミジア・ニューモニアに起因する心臓疾患の処置方法

(57)【要約】
有効量のマクロライド抗生物質、例えばアジスロマイシンなどのアザライドを、所望により一つ以上の薬理的に許容される担体または賦形剤とともに、被検者に投与することからなる、アテローマ動脈硬化症の克服方法。

【特許請求の範囲】

1．　有効量のマクロライド抗生物質を、所望により一つ以上の薬理的に許容される担体または賦形剤とともに、被検者に投与することからなる、アテローマ動脈硬化症の克服方法。

2．　第一の有効量のアジスロマイシン投与の約１か月後に、第二の有効量のアジスロマイシンを投与する、請求項１に記載の方法。

3．　一つまたはそれ以上のさらなる有効量のアジスロマイシンを、１か月またはそれ以上の間隔で追加する、請求項２に記載の方法。

4．　アテローム動脈硬化症の克服に用いられる薬剤の製造への、アジスロマイシンまたはその誘導体の使用。

【発明の詳細な説明】

クラミジア・ニューモニアに起因する心臓疾患の処置方法

発明の分野

本発明は、心臓疾患の処置に関し、特にアテローム動脈硬化症の克服における特定の抗生物質の使用に関する。

従来技術の説明

冠状心臓疾患は、西側世界における未熟死の最も大きな一つの原因であり、英国だけでも、毎年約160,000人の死亡を招いている。医学専門の重要な割合を占める伝統的な見方は、年令、および社会的、経済的要因が、心臓疾患の主要な原因であるということである。しかしながら、近年、冠状心臓疾患には特定の細菌が関連しているという非常に多数の報告がなされているが、これらは、ある方面ではかなり懐疑的に受け止められている。

このような報告で言及された細菌としては、ヘリコバクター・ピロリ(Helicobacter pylori)およびクラミジア・ニューモニア(Chlamidia pneumoniae)が挙げられる。すなわち、例えば、１９８０年後半にフィン族研究者は、冠状心臓疾患患者がクラミジア・ニューモニア細菌に対する抗体を高レベルで有することが、健康な人よりもありがちであったと報告した(The Lancet, 1988:983-986)。より最近になって、微生物そのものが、腹大動脈修復を受けた患者のアテローム硬化動脈中に見出された(J. Clin. Pathol., 1996, 49(2):102-106)。The Journal of the American College of Cardiology, June 1996, 27(7) : 1555-61において、アテローム硬化性斑を外科摘出された患者の79％が病巣中で活性なクラミジア・ニューモニアに対する抗体を示したが、非アテローム硬化性病理試料の僅か４％だけが同じ抗体を示したことが報告された。これに基づいて、細菌はアテロームと結び付けることができるが、動脈損傷の他の原因とは結び付けることができないと主張された。

他の研究者は同様な知見を報告しており、動脈壁の持続性細菌感染を伴う炎症は、血液中のフィブリノーゲンおよび組織因子のレベルを上昇させ、かつアテローム血栓症の可能性を増加させる免疫反応の引き金となりうることが示唆された

。

しかしながら、医学専門家は、特に心臓学者の間では、この理論に関して未だにかなり懐疑的であり、多くの研究者は、クラミジア・ニューモニアが罹患した心臓に多少とも存在しているのか、あるいは、もしそうであっても、無実の傍観者として存在するにすぎないのかを疑っている。すなわち、the Journal of Infectious Diseases, 1996, 173(4) : 957-62には、研究チームが58のアテロームサンプルからクラミジア・ニューモニアを培養できなかったことが報告されている。従って、心臓疾患におけるクラミジア・ニューモニアの役割については、もし役割があるとしても、意見が確固として分かれている。

本発明は、特定の抗生物質、より詳しくはアジスロマイシン(azithromycin)などのマクロライド(macrolide)抗生物質を投与する

ことにより、多分、基礎をなすクラミジア・ニューモニア感染の根絶によって、心筋梗塞後の患者の血液中における血栓および炎症のマーカーを減少させ得るという予想外の知見に基づくものである。従って、このようなマクロライド抗生物質の投与は、例えば心臓組織の炎症、血栓、喉頭炎に対する感受性、再入院の可能性および／またはバイパスまたは他の外科的処置の必要性を減少させることにより、心臓病患者にとって有益であるだけでなく、予防的に一般の患者にとっても有益である。

発明の概要

従って、一つの観点から見ると、本発明は、有効量のマクロライド抗生物質、例えばアザライド(azalide)を、所望により一つ以上の薬理的に許容される担体または賦形剤とともに、被検者に投与することからなる、アテローム動脈硬化症の克服方法を提供する。

本発明に係る方法において、マクロライド抗生物質は、所望により、他の有用な物質、例えば血小板凝集阻害剤、血液希釈剤、および／または脂質低下剤とともに投与することができる。従って、もう一つの観点において、本発明は、マクロライド抗生物質またはその誘導体、例えばアジスロマイシンを、血小板凝集阻害剤、血液希釈剤、および／または脂質低下剤などからなる群から選択された一

つ以上の物質とともに、所望により一つ以上の担体または賦形剤とともに含有する、アテローム動脈硬化症を克服するための組成物を提供する。

もう一つの観点から見ると、本発明は、アテローム動脈硬化症の克服に用いられる組成物の製造への、マクロライド抗生物質、例えばアジスロマイシン、またはその誘導体の使用を提供する。

よく知られているように、マクロライド抗生物質は、一つ以上の糖分子が結合したマクロ環状ラクタム環の存在を特徴としている。このような抗生物質の代表例としては、エリスロマイシン(erythromycin)、スピラマイシン(spiramycin)、オレアンドマイシン(oleandomycin)、クラリトロマイシン(clarithromycin)、ジリトロマイシン(dirithromycin)、ロキシトロマイシン(roxithromycin)、ジョサマイシン(josamycin)、キタサマイシン(kitasamycin)、ミデカマイシン(midecamycin)、ミオカマイシン(miocamycin)、ロキタマイシン(rokitamycin)、ロザラマイシン(rosaramycin)、アジスロマイシン(azithromycin)、およびこれらの誘導体、例えばリン酸塩などの塩、およびアセテートなどのエステルが挙げられる。二水和物の形態で Zithromycin®として商業的に入手しうるアジスロマイシン[(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-(2,6-ジデオキシ-3-C-3-O-ジメチル-α-L-リボヘキソピラノシルオキシ)-2-エチル-3,4,10-トリヒドロキシ-3,5,6,8,10,12,14-ヘプタメチル-11-(3,4,6-トリデオキシ-3-ジメチルアミノ-β-D-キシロヘキソピラノシルオキシ)-1-オキサ-6-アザシクロペンタデカン-15-オン]が、本発明に係る使用のために好ましいマクロライドまたはアザライド抗生物質であり、３日間の短期間に毎日１回の投与の使用が効果的であることが証明

された。このような簡単な摂生法は、患者のコンプライアンス（応諾）を保証するのに極めて有利であることが評価される。

マイクロライド抗生物質、例えばアジスロマイシンの典型的な一日投与量は、所望により他の投与量および投与方法を採用してもよいが、例えば三日間程度経

口投与にて500mgであろう。処置効果を最大にするために、第一コースの後、いくらかの期間、例えば一、二または三ヶ月での抗生物質の第二コースを与えることが都合よい。この利益を持続させるために、第二コース後、一、二または三ヶ月の間隔で抗生物質のさらなるコースを与えることが、より都合よい。典型的には、最初のコースを投与した後、一年間程度までこれを行う。

ここで、本発明を実施例を用いて非限定的に説明する。

実施例１

６０人の心筋梗塞後の患者をアジスロマイシン（一日に500mg、三日間経口的に与えられた）またはプラセボで処置する、ランダム化された二重盲見研究を行った。さらに三ヶ月後、４５人の患者にアジスロマイシンまたはプラシーボのさらなる盲見コースを与えた。この結果は、アジスロマイシン、特に二重治療後のアジスロマイシンが、Chlamydia pneumoniae抗体力価（IgG）における有意な減少および単球組織因子、CD11b発現、および全白血球カウントおよび血清ネオプテリン量などの凝固充進および炎症の血清マーカーの低減されたレベルを導くことを示した。

実施例２

心筋梗塞（MT）からの生存男性において、抗Chlamydia pneumoniae（Cp）に対する抗体および将来的な心臓血管障害発症に対する抗体間の関係を調査した。アジスロマイシン抗生物質治療の効果を、MI後の患者のサブグループにて評価した。

1995年２月から1995年９月までの間に、LondonのSt.George,s HospitalでのMI後の外来診察室に通院した継続的男性患者220人が登録された。試験抗原としてCp株IOL-207の基本小体を用いたマイクロ免疫蛍光アッセイにより、Cpに対する血清IgG抗体に関して、患者をスクリーニングした。慢性気管支炎患者、そのときマクロライド抗生物質を摂取していた人、および先の６ヶ月以内にMIであった人（梗塞に起因する免疫反応の消散を確実にするため）を除外した。Chlamydia trachomatis抗原またはChlamydia psitticai抗原と交差反応した血清を有する被献者も除外した。患者を以下の三つの抗Cp抗体力価グループの一つに区分した：検

出できる抗Cp抗体がない(血清反応陰性)Cp-veグループ(n=59)；1/8から1/32の間の血清希釈度で血清反応陽性のCp-Iグループ(n=74)；および1/64以上の血清希釈度で血清反応陽性のCp+ve(n=80)。抗Cp抗体力価を、後者のグループでは３ヶ月後に再測定した。両方の場合でのCp力価（６４において１以上）を有する患者は、プラセボ制御された、アジスロマイシン治療(三日間の500mg/dまたはこのようなコースを三ヶ月離して二回のいずれか)のMI後の患者における、抗Cp力価に対する効果、および止血および炎症マーカーに対する効果の二重盲見研究に参加した。これらの患者は、自身の抗Cp力価、および三ヶ月および六ヶ月で試験し

た他のマーカーを持っていた。

有害心臓血管障害発症（致命的でないMIによる病院への最初の入院；静脈内抗アンギナ治療、冠状血管形成、または緊急冠状動脈バイパス手術のいずれかを必要とする不安定なアンギナ；あるいは心臓血管死として定義される）を、最初のCp力価測定から１８ヶ月間監視した。情報は、患者の診察室訪問、電話による照会、ケースノートおよび病院で電算機化処理された記録から得られた。

統計的分析

有害障害発症の頻度を、Cp-ve、Cp-IおよびCp+veグループにおいて評価した。さらに、Cp+ve患者を三つのサブグループに分けた。即ち、抗生物質研究に参加しなかった患者Cp+ve-NR；ランダムにプラセボ薬物処理した患者Cp+ve-P；およびアジスロマイシンの一つのまたは二つのクールのいずれかを与えた患者Cp+ve-Aである。

有害障害発症を経験した患者の比率を、Cp-veグループおよび他の全てのグループ間でχ^2試験を用いて比較した。Cp-veグループに匹敵するCp+veグループのおのおのにおける有害心臓血管障害発症のORを、年齢、糖尿症、高血圧、脂肪過剰血症、喫煙状態（現在、過去、全くなし）および最終冠状動脈バイパス手術または経皮経内腔冠状血管形成（percutaneous transluminal coronary angioplasty）(STATA分析)に関して補正する前および後の多重論理回帰モデルを用いて計算した。P<.05の値を、有意性ありと考慮した。

結果

七人の患者を、血清が他のクラミジア種と交差反応したために除外した。したがって、分析は残る213患者ベースである。表１は、臨床的特徴のベースラインを示す。1/64以上の血清反応陽性が持続している患者は、経口のアジスロマイシン（Cp+ve-A、三日間で500mg/d[n=28]または六日間で500mg/d[n=12]）またはプラセボ（Cp+ve-P、n=20）のいずれかをランダムに施された。残る１２人の患者のうち、７人はこの試験に参加する意志がなく、５人は彼らの参加を妨げるような他の厳しい医療状態にあった。

表１　-18±4 月間の追跡における平均での患者特性および心臓血管障害発症率

グループ	Cp-ve (n=59)	Cp-I (n=74)	Cp+ve-NR (n=20)	Cp+ve-P (n=20)	Cp+ve-A (n=40)
年，y(平均±SD)	63±8	61±9	63±9	60±9	58±7
糖尿病，n(%)	6(10)	9(12)	6(30)	8(40)	12(30)
高血圧，n(%)	15(25)	9(12)	3(15)	4(20)	7(18)
最終PTCAまたはCABG，n(%)	12(20)	20(27)	8(40)	6(30)	12(30)
脂肪過剰血症，n(%)	23(39)	31(42)	10(50)	7(35)	18(45)
喫煙（過去），n(%)	39(66)	40(54)	14(70)	10(50)	21(53)
喫煙（現在），n(%)	7(12)	16(22)	3(15)	5(25)	14(35)
MI後の月，平均±SD	44±14	44±27	46±32	39±24	47±32
MI前，%	53	53	50	58	53
放出部分，%	41±14	45±13	41±19	47±14	48±14
有害心臓血管障害発症，n					
死亡	0	0	1	1	1
不安定アンギナ/MI	0	7	4	4	2
PTCA/CABG	4	4	1	0	0
合計 (%)	4(7)	11(15)	6(30)	5(25)	3(8)
χ^2 対 Cp-ve		2.1	7.3	4.9	0.9
p		.1	.007	.03	NS

Cp-ve は患者の血清陰性グループ；Cp-I は中間抗体価を有するグループ；Cp+ve-NR/P はプラセボに対してランダム化されたか、またはランダム化されない上昇した抗体価を有するグループ；Cp+ve-A はアジスロマイシンに対してランダム化された上昇した抗体価を有するグループ；PTCA は経皮経内腔冠状血管形成；および CABG は冠状動脈バイパス手術である。

6ヶ月目、抗体試験に関連した患者においては、抗-cp価が、プラセボ(P=.02)を摂取した患者がたった10%(20の内2)であったのと比較して、アジスロマイシンを投与された患者の43%において≦1/16となった。有害

動脈障害発症に対するORは、全てのグループに付いて、表2に示した。有害障害

発症の頻度は、抗-Cp価の上昇とともに増加し、交絡値（confounding variables）に対する補正後に持続した。Cp+ve-NRおよびcp+ve-pグループ間で、心臓血管危険ファクタまたは障害発症における有意な差異がなかったため、この二つのグループは、ORの計算において加算された。Cp+ve-Aグループにおける更なる心臓血管障害発症率は、cp-veグループと同様であった(8%対7%；OR, 0.9；P=NS)。加算されたプラセボ／非ランダム化グループにおける患者と比較して、アジスロマイシン処置グループは、0.2のOR（95%信頼区間, 0.05～0.8；P=.03）とともに、５倍の減少を有していた。一回または二回アジスロマイシンコースを受けた患者の間では、抗-cp価または心臓血管障害発症率での減少を有する比率において差異がなかった。

表２-血清反応陰性および血清反応陽性患者グループにおけるCV障害発症に対するOR

グループ	合計CV障害発症 n(%)	未調整 OR (95% CI)	調整 OR (95% CI)
Cp-ve(n=59)	4(7)		
Cp-I(n=74)	11(15)	2.4(0.7-8.0)	2.0(0.6-6.8)
Cp+VE-NR/P(n=40)	11(28)	5.2(1.5-17.8)*	4.2(1.2-15.5)†
Cp+ve-A(n=40)	3(8)	1.1(0.2-5.3)	0.9(0.2-4.6)

グループ表示の説明に付いては表１参照

心臓血管(CV)障害発症の比較は、全てのグループに付いて、グループCp-veに対するものである(ORと表す(95%信頼区間[CI]))。調整ORは、以下の値：年齢、糖尿病、喫煙状態、高血圧症、脂肪過剰血症および最終冠状血管再生、を調節した後に計算。

★P=.008、

+.03対グループCp-ve。

【国際調査報告】

INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/GB 97/02862

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 22819 A (BOARD OF REGENTS OF THE UNIVERSITY OF WASHINGTON) 23 December 1992 see page 3, line 31 - line 35 see page 9, line 9 - line 34 see page 16, line 23 - line 28 see page 22 see page 25 lines 33-34,37-39 ---	1-4
X	MARRIE: "Chlamydia pneumoniae" THORAX, vol. 48, no. 1, 1993, see page 2, right-hand column see page 3 --- -/--	1,4

[X] Further documents are listed in the continuation of box C.　　[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 1998	11.03.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Gac, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna　al Application No
PCT/GB 97/02862

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COOK : "Chlamydia pneumoniae" J. ANTIMICROB. CHEMOTHER., vol. 34, no. 6, December 1994, pages 859-73, XP002056252 see page 865	1,4
X	COOK: "Clinical aspects of Chlamydia pneumoniae infection" PRESSE MED. (FR.), vol. 24, no. 5, 4 February 1995, pages 278-282, XP002056253 see page 280, right-hand column see page 281	1,4
X	VALTONEN: "Symposium graft infection sponsored by the Sanofi-Chinoin Co: the causative role of Chlamydia pneumoniae and other bacteria in the development of coronary heart disease" INT. ANGIOLOGY, vol. 15, no. 2supl, May 1996, page 61 XP002056254 abstract nr 034	1,4
X	BLANCHARD: "Chlamydia infections" BR. J. CLIN. PRACT., vol. 48, no. 4, 1994, pages 201-205, XP002056255 see page 202; table 1 see page 203, left-hand column see page 204, left-hand column	1,4
X	GAYDOS: "Chlamydia pneumoniae: a review and evidence for a role in coronary artery disease" CLIN. MICROBIOL. NEWSLETTER, vol. 17, no. 7, 1995, pages 49-54, XP002056256 see page 51	1,4
P,X	STILLE: "Argumente für eine Antibiotika-Therapie der Atherosklerose" CHEMOTHER. J., vol. 6, no. 1, 21 April 1997, pages 1-5, XP002056257 see the whole document	1,4

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte .ional application No.
PCT/GB 97/ 02862

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-3
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-3 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern nal Application No
PCT/GB 97/02862

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9222819 A	23-12-92	AU 2249892 A	12-01-93
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		ZA 9206713 A	09-03-93

Form PCT/ISA/210 (patent family annex) (July 1992)

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(81)指定国　　EP(AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OA(BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), AP(GH, KE, LS, MW, SD, SZ, UG, ZW), EA(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW